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SOX10 and the Tendency of Perineural Invasion in Salivary Gland Adenoid Cystic Carcinoma

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ABSTRACT

Background
Adenoid cystic carcinoma is a malignant salivary gland tumor with unique features, including slow growth, progressive, poor prognosis, recurrence propensity, and perineural invasion tendency. SOX10 is a transcription factor expressed in the majority of tumors. SOX10 overexpression was hypothesized to play an important role in tumor-stroma interactions, especially perineural invasion and histopathological patterns.

Methods
A cross-sectional study was performed using 30 blocks of formalin-fixed embedded specimens previously diagnosed as salivary gland adenoid cystic carcinomas. Perineural invasion and histopathological patterns were evaluated followed by immunohistochemical staining to evaluate SOX10 expression. The staining intensity and proportion of positively stained cells in both tumor and stroma cells were grouped into high and low expression levels. Chi-square tests were used for statistical analysis.

Result
The cribriform pattern was the most common histopathological pattern in both high and low SOX10 expression. The majority of tumors with high SOX10 expression (66.67% in stroma cells and 73.33% in tumor cells) were found to have more perineural invasion.

Conclusion
There was a tendency for perineural invasion in tumors with high SOX10 expression, although this was not statistically significant. There was no significant association between SOX10 expression and histopathological pattern.

Keywords: adenoid cystic carcinoma, histopathological pattern, perineural invasion, SOX10

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INTRODUCTION

Salivary gland adenoid cystic carcinoma comprises 10% of all salivary gland malignant tumors and 1% of head and neck malignancies. The incidence was reported 2 cases per 100,000 people per year in the United States. The mean age at diagnosis was 57 years old, with no ethnic predisposition, and the sex ratio of women to men was 1.5:1.3. The mean age incidence is reported at 46.3 years old in Medan-North Sumatra.[1-4]

This tumor is characterized by slow growth, progressive, and often painful because of its tendency for neural invasion, local recurrence, and distant metastases; hence, it is classified as a tumor with the potential for destruction and unpredictable outcomes. The clinical and pathophysiological nature of this tumor is not fully understood, resulting in difficulties in the development of therapeutic targets.[1,2,5]

Adenoid cystic carcinoma occurs in both the major and minor salivary glands. It consists of heterogeneous cells, i.e.: epithelial (luminal) cells and myoepithelial (abluminal) cells. Histologically, these tumors are classified into tubular, cribriform, and solid patterns. Solid patterns are associated with a poor prognosis, compared to the other.[6]

SOX10 is a major transcription factor related to epithelial-mesenchymal transition (EMT), invasion, and metastasis. This marker is expressed in adenoid cystic carcinoma cells and tumor stem cells, indicating features of neural crest stem cells. This property facilitates PNI events via Schwann-like differentiation. Chun San et al reported that Schwann cells can induce EMT on adenoid cystic carcinoma cells culture and hypothesized an increased PNI event.[7] However, few research on the association of SOX10 to PNI on human adenoid cystic carcinoma was carried out. This study aimed to determine the correlation between SOX10 expression, perineural invasion, and histopathological patterns of salivary gland adenoid cystic carcinoma.

METHODS

A cross-sectional study performed using 30 fixed formalin paraffin embedded of human adenoid cystic carcinoma was obtained from Dr. M. Djamil Hospital and Sentra Diagnostik Patologi Anatomik Universitas Andalas between the period of January 2017 to December 2022. Hematoxylin and eosin (HE) staining was used to evaluate histological patterns and PNI. Perineural invasion was classified as positive or negative, and the World Health Organization (2017) criteria were used to classify the tumor histological patterns. Immunohistochemistry for SOX10 was performed (EP268, Rabbit Monoclonal Primary Antibody, Cell Marque, dilution 1:200).

Histological analysis was done using an Olympus CX23 microscope at 100x and 400x magnification. Perineural invasion was considered to be positive when tumor cells were found to encircle of minimum one-third of the neural circumference or directly invade the nerve. The histopathological pattern was grouped into tubular, cribriform, and solid.

SOX10 was immunohistochemically expressed as brown nuclear staining in tumor and stroma cells. SOX10 Immunohistochemistry was evaluated using the following criteria: colorless (0), buff (+1), brownish yellow (+2), and dark brown (+3).[8] The number of positively stained cells/100 cells at each intensity was determined. The scores ranging from 0 to 300 were calculated using the H-score system. The counting was applied three times in each sample. The areas of tumor and stroma cells assessed were selected randomly. The average score was used. The cut-off value for SOX10 level was chosen based on the median H-score for each tumor and stroma cell. An optimal cutoff value was identified: low expression level less than and high expression level more than the median H-score. The median scores for tumor and stroma cells were 244 and 35.34, respectively.

RESULT

Characteristics of research samples

The youngest age to have adenoid cystic carcinoma in our study was 28 years old, and the oldest was 68 years old. The tumors were commonly found at the age of 41-50 (36,7%), with a mean age of 45,57 years old. Females were more common than males, with a ratio of 2:1. Minor salivary glands were the most common (70%). The majority of the samples had perineural invasion (53,3%), lymphovascular invasion (63,3%), and cribriform histopathological patterns (70%). The sample characteristics are listed in Table 1.

SOX10 Expression in Tumor and Sroma Cells

Photomicrographs of HE and immunohistochemical staining are shown in Figure 1. The semi-quantitative H-score measurements of SOX10 expression in tumor and stroma cells are listed in Table 2.

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Table 1. Characteristics of research samples.

Characteristics	Total	
	Number (n=30)	%
Age group (years old)		
0-10	0	0
11-20	0	0
21-30	4	13.3
31-40	6	20
41-50	11	36.7
51-60	5	16.7
61-70	4	13.3
71-80	0	0
81-90	0	0
>90	0	0
Gender		
Male	10	33.3
Female	20	66.7
Tumor location		
Mayor salivary gland	9	30
Minor salivary gland	21	70
Type of specimen		
Exicion (parotidectomy, lobectomy, and wide excision)	18	60
Biopsy	12	40
Perineural invasion		
Negative	14	46.7
Positive	16	53.3
Lymphovascular invasion		
Negative	11	36.7
Positive	19	63.3
Histopathological pattern		
Tubular	3	10
Cribriform	21	70
Solid	6	20
SOX10 expression in tumor cells		
Low	15	50
High	15	50
SOX10 expression in stroma cells		
Low	15	50
High	15	50

Table 2. Characteristics of research samples and semi-quantitative H-score measurements of SOX10 expression in tumor and stroma.

7	G	PNI	HP	SOX10 stroma cells level	SOX10 tumor cells level
68	M	+	S	L	L
28	F	+	C	H	H
36	F	-	C	H	L
65	M	-	C	L	L
40	F	-	C	H	L
42	F	+	T	H	H
42	F	-	S	L	L
58	M	+	S	H	L
36	F	+	C	L	L
56	F	+	S	H	H
67	F	-	C	L	L
46	F	-	S	H	L
45	F	+	S	L	H
42	F	+	C	L	H
45	M	-	C	L	L
48	M	+	T	H	H
46	M	+	C	H	L
55	F	+	C	L	H
66	F	+	T	L	L
54	M	-	C	L	L
50	F	+	C	H	H
41	F	-	C	L	L
33	M	-	C	L	H
55	M	+	C	H	H
48	F	-	C	H	L
35	F	+	C	H	H
34	M	-	C	L	H
30	F	-	C	L	H
28	F	+	C	H	H
28	F	-	C	H	H

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The Correlation of SOX10 Expression to Perineural Invasion

There was a tendency for perineural invasion on tumors with high SOX10 expression. However, there was no significant correlation of SOX10 expression to perineural invasion by Chi-square test with continuity correction test results of p=0.067 (tumor) and p=0.272 (stroma) list in Table 3.

Table 3. The correlation of SOX10 expression to perineural invasion.

SOX10 Expression	Perineural Invasion		n (%)	*p-value*
	Negative f (%)	Positive f (%)		
Tumor cells				
Low	10 (66.7)	5 (33.3)	15 (100)	0.067
High	4 (26.7)	11 (73.3)	15 (100)	
Stroma cells				
Low	9 (60)	6 (40)	15 (100)	0.272
High	5 (33.3)	10 (66.7)	15 (100)	

The correlation of SOX10 Expression to histopathological pattern

Most samples with cribriform patterns showed both low and high SOX10 expression. Bivariate analysis with Pearson Chi-square test result p=0.592 (tumor) and p=0.827 (stroma) show in Table 4. There was no significant correlation of SOX10 expression to the histopathological pattern.

Table 4. The correlation of SOX10 expression to perineural invasion.

SOX10 Stroma Peritumoral Expression	Growth Pattern			n (%)	*p-value*
	Tubular f (%)	Kribriform f (%)	Solid f (%)		
Tumor cells					
Low	1 (6.7)	10 (66.7)	4 (26.6)	15 (100)	0.592
High	2 (13.3)	11 (73.4)	2 (13.3)	15 (100)	
Stroma cells					
Low	1 (6.67)	10 (66.67)	3 (20)	15 (100)	0.827
High	2 (13.33)	10 (66.67)	3 (20)	15 (100)	

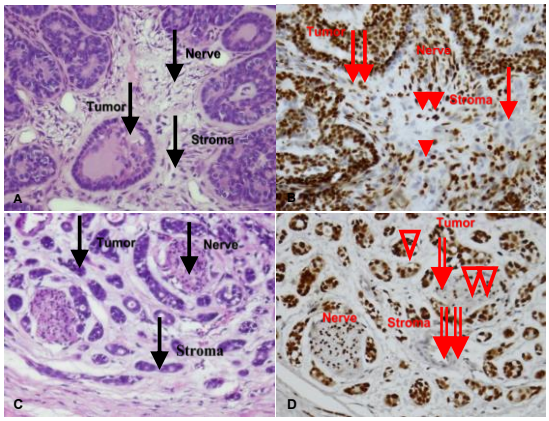

Figure 1. Hematoxylin-eosin staining (A, C) and immunostaining of SOX10 expression in tumor and stroma cells (B, D). SOX10 expression in stroma cells, arrow: colourless (0); arrowhead: buff (+1); double arrow: brownish yellow (+2); double arrowhead: dark brown (+3). SOX10 expression in tumor cells; open arrow: colorless (0); open arrowhead: buff (+1); double open arrow: brownish yellow (+2); double open arrowhead: dark brown (+3). B and D: Tumors with high SOX10 expression. Magnification 400 times.

DISCUSSION

The age characteristics of the samples in this study are similar to of those Siregar et al, where the highest incidence in 4th decade of life with a mean age in this study was 45.57 years old. A study by Daniel Monteiro et al revealed the highest incidence, with a mean age 55.8 years old. Epidemiological studies have shown that this tumor was most common in the 4th-5th decade. Aging is associated with functional cycle changes in the salivary gland, and overexpression of MYB has an estimated impact on DNA repair, apoptosis, cell migration, and cell cycle signalling. Xu et al and Rettig et al revealed the one of oncogenetic mechanism of this tumor by increasing MYB and NFIB expression.[4,9-12]

Females were the most common with ratio female:male is 2:1. It is similarly with Mark Zupancic et al. Ximema Mimica et al revealed the gender is correlate with survival. Female have better outcomes and higher survival rates. Comorbid disease, smoking behaviour, and androgen receptor is correlated to poor prognosis and survival in male.[13,14]

The location of the primary tumor and lymphovascular invasion correlated with

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metastasis. R. Min et al revealed about 10% adenoid cystic carcinoma with metastasis. The base of the tounge (19.2%), tongue (17.6%), and base of the mouth (15.3%) frequently metastasized to the cervical lymp node. Minor salivary glands, particularly the buccal mucosa, were frequently found in our study. This is different from the study by Zupancic et al, in which the parotid gland was the most frequent. About 450-750 minor salivary glands spread over a long aerodigestive tract, and half of them had a malignant tumor. Lymphovascular invasion is considered as strong predictor to lymp node metastasis, therefore selective dissection must be considered.[14-16]

This study revealed a solid pattern (83.33%) with LVI. Lanlan Xuan et al showed that the predominant solid pattern has high malignant transformation, LVI, necrosis, a Ki-67 index ≥30%, and advanced disease. Specimens of adenoid cystic carcinoma commonly have small specimens and fragmented due to tumor infiltrative growth. This can make it difficult to assess the surgical margins, perineural invasion, and lymphovascular invasion.[6]

Adenoid cystic carcinoma prone to perineural invasion. Tumors damage the blood-nerve barrier and infiltrate the nerve in the tumor microenvironment. Stroma components contribute to tumor progression and survival. Tumor-stroma interaction remodels the tumor microenvironment. Mesenchymal stem cells is one of the micro microenvironmental components. It can be influenced by Notch1 signalling from adenoid cystic carcinoma cells to Schwann cell-like differentiation. This process is initiated by an activated neural crest property.[10,17-20]

The SOX10 is a major transcription factor that role-play in the maintenance, migration, and development of the neural crest cells. SOX10 expression profile associated with neural crest stemness suggests that neural crest signalling is critical in adenoid cystic carcinoma. The current study revealed that this protein is expressed in 90% of tumors. Myoepithelial cells derived from the neural crest surround the acini and ducts of several exocrine glands, including the salivary glands. These cells expressed higher levels of SOX10 than epithelial cells.[21,22]

Epithelial-mesenchymal transitition contributes to the invasion process, including perineural invasion. Chun San et al showed Schwann cell promote EMT and the Schwann-like differentiation of adenoid cystic carcinoma cells culture. Epithelial tumor cells express various marker that promote EMT and changes in epithelial and stroma cells. This tumor has a signature SOX10 gene expression is considered impact to perineural invasion.[7,23,24]

CONCLUSSION

The majority of perineural invasion was found in high SOX10 expression both in peritumoral stroma cells (66.67%) and tumor cells (73.33%). The cribriform pattern was the most common histopathological pattern in either high or low SOX10 expression. Based on the H-score, there was a tendency for perineural invasion in high SOX10 expression. However, there was no significant association between SOX10 expression with perineural invasion and histopathological patterns.

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